American Journal of Medical Genetics 66:449–452 (1996)

Brachmann-de Lange Syndrome: Autosomal Dominant Inheritance and Male-to-Male Transmission

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We report on familial occurrence of the Brachmann-de Lange syndrome (BDLS): a mildly affected father and his severely affected son and daughter who have different mothers. Both children are severely affected while the father has a much milder but definite BDLS phenotype. Our report documents the third example of male-to-male transmission and adds to the argument against exclusively maternal transmission in familial cases. In addition, our findings illustrate the occurrence of severe manifestations in cases of familial BDLS. © 1996 Wiley-Liss, Inc.

KEY WORDS: Brachmann-de Lange syndrome (BDLS), autosomal dominant, male-to-male transmission, exclusively maternal transmission

INTRODUCTION

Brachmann-de Lange syndrome (BDLS), described independently by Brachmann [1916] and de Lange [1933], is a multisystem, multiple congenital anomaly, growth, and neurodevelopmental retardation syndrome. Though variable in expression, the condition is recognized on the basis of synophrys, elongated eyelashes, and down-turned vermillion borders. Over 300 cases have been described and the incidence is estimated at 1/10,000 [Beck, 1976] to 1/60,000 [Opitz, 1985, 1994]. Phenotypic overlap has been observed with trisomy 3q [Falek et al., 1966; Wilson et al., 1978; Sciorra et al., 1979; Van Essen et al., 1991; Wilson et al., 1985; Holder et al., 1994] and a de novo balanced translocation t(3;17) [Ireland et al., 1991]. The ratio of affected males to females is equal. Although both recessive and dominant inheritance patterns have been reported, most BDLS cases are sporadic [Jackson et al., 1993]. Two previously reported hypotheses regarding expressivity and cause assert that 1) familial BDLS is associated with a milder phenotype than sporadic cases and 2) in dominant familial BDLS, transmission is exclusively maternal in origin [de Die-Smulders et al., 1992; Feingold and Lin, 1993; de Die-Smulders and Theunissen, 1994]. To date, there are seven reports of autosomal dominant transmission [Beck 1974; Kumar et al., 1985; Leavitt et al., 1985; Robinson et al., 1985; Reid et al., 1991; de Die-Smulders et al., 1992; Feingold and Lin, 1993]. Two cases of male-to-male transmission have been reported: one family including three sibs and the father with microcephaly, metatarsus adductus, developmental delay, and a facial appearance reminiscent of mild BDLS [Halal and Silver, 1992] and a second, recently reported case of mild BDLS in a father and son with developmental delay, facial anomalies, and brachydactyly [Chodirker and Chudley, 1994]. Our family represents the eighth published example of autosomal dominant inheritance of BDLS and illustrates not only male-to-male transmission, but also the occurrence of a severe phenotype in multiple offspring of a mildly affected parent.

CLINICAL REPORT

The propositus (patient A) presented as a 4-hour-old Latin American boy born to a 22-year-old G1 Latin American woman and her 34-year-old nonconsanguineous mate. Good prenatal care was received. Repeat ultrasound studies noted IUGR. An ultrasound performed at 36 weeks of gestation showed a unilateral diaphragmatic hernia. Spontaneous labor began at 37 weeks and patient A was delivered vaginally in a vertex position. He required intubation and ventilation due to lack of respiratory effort at delivery. Apgar scores were 9 at 1 minute and 8 at 10 minutes. He was SGA with birth weight of 2,080 g (<3rd centile), length of 45 cm (<3rd centile) and OFC of 29 cm (1 S.D. below 3rd centile). Facial appearance was consistent with a diagnosis of BDLS, including small palpebral fissures, generalized hirsutism, long curled eyelashes, synophrys,

Received for publication December 11, 1995; revision received February 26, 1996.

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small nose with anteverted nares, thin down slanting vermillion borders, circumoral cyanosis ("teint bleuâhre" as Cornelia de Lange called it), and micrognathia (Fig. 1). He also had a high arched palate and apparently low-set ears with abnormal helices. He also had multiple limb contractures, small hands and feet, bilateral transverse palmar creases, fifth finger clinodactyly, mild genua vara, and rockerbottom feet. Echocardiogram showed tetralogy of Fallot with a large VSD, aortic override, and mild pulmonic stenosis. Chest roentgenogram confirmed presence of a unilateral diaphragmatic hernia with ipsilateral pulmonary hypoplasia. ABR showed bilateral mild hearing loss of primarily a conductive component. The patient failed to thrive due to gastrointestinal reflux and died at age 5 months. Chromosomes were normal (46,XY).

The sister of the index case (patient B) is a 5½-year-old girl. She was born at term and was SGA (birth weight of 1,500 g). She required intubation and ventilation due to lack of respiratory effort at birth. It is unknown how long ventilation was necessary. She was monitored after discharge from the hospital and was noted to have a heart murmur, two episodes of seizure activity, and bilateral hearing loss. She was hospitalized intermittently during the first 2 years of life for feeding difficulty, chronic emesis, weight fluctuation, and failure to thrive. Physical findings include hirsutism, synophrys, long curled eyelashes, ptosis, anteverted nares, thin, down slanting vermillion borders, and teint bleuâhre (Fig. 2). There is no oligodactyly but some flexion contractures as well as genua vara. Development is significantly delayed, at 5½ years, the patient has no expressive language but responds to sounds and simple commands. She sat and walked at age 4.5 years. Chromosomes were normal (46,XX).

Patient C is a 34-year-old Latin American man and father of patients A and B who have different mothers. He is 1.75 m tall and weighs 86 kg. He reports that he is in good general health and has no problems with vision or hearing, but had scoliosis, back problems, and feeding problems accompanied by gastrointestinal reflux. He reports a chronic history of upper respiratory tract infections and congestion. On physical examination he has low posterior and anterior hairlines, prominent synophrys, long curled eyelashes, a long philtrum, thin down turned vermillion borders, and micrognathia (Fig. 3). His ears are simple and low-set. Examination of his hands suggests brachydactyly and proximally placed thumbs. His feet are relatively small but with no apparent abnormalities. He reports finishing the 10th

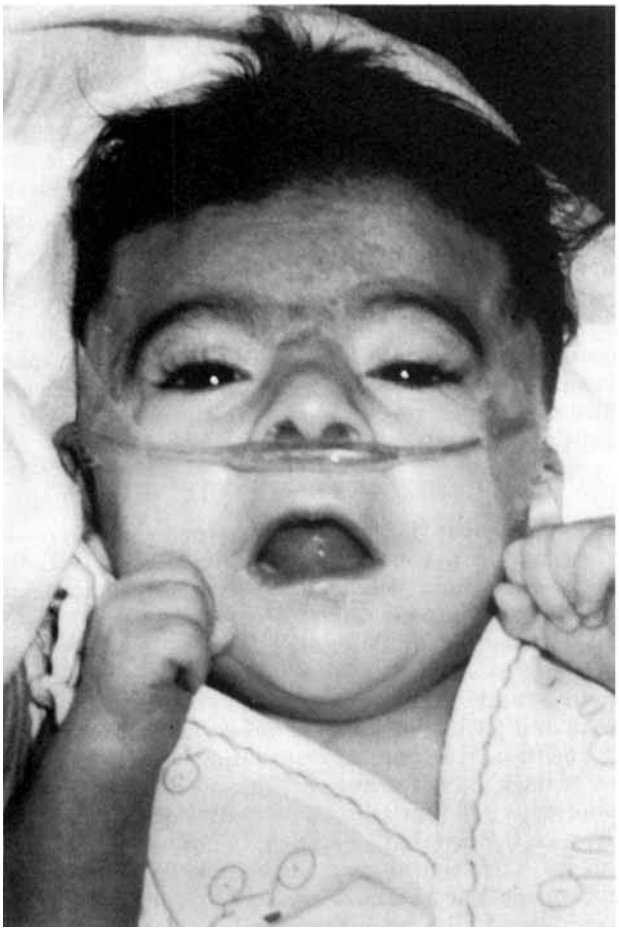

Fig. 1. Patient A, the index case.

Fig. 2. Patient B, half-sister of patient A.

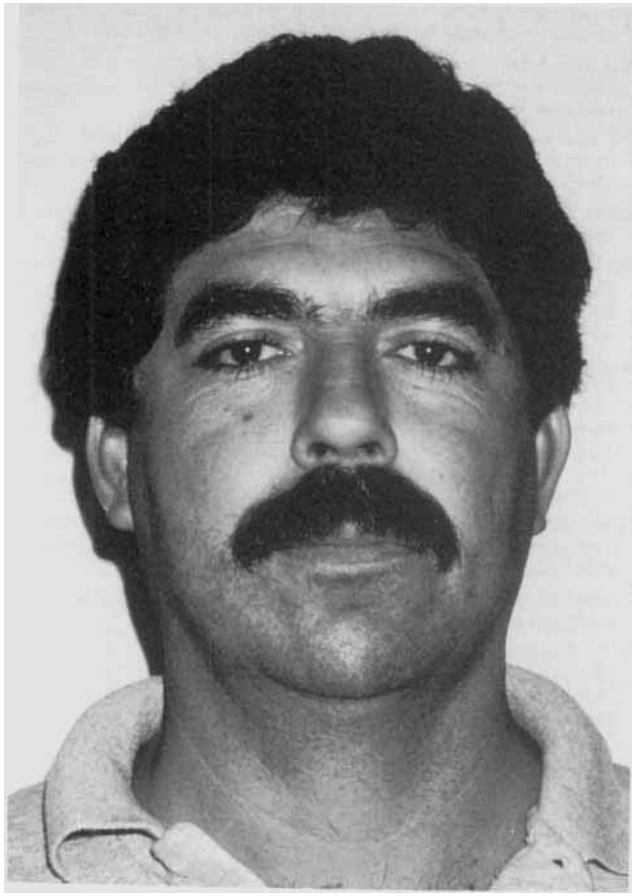

Fig. 3. Patient C, father of patients A and B.

grade of high school with no problems or special assistance required. Chromosomes were normal (46,XY).

DISCUSSION

Over 300 cases of BDLS, both sporadic and familial, have been described. Phenotypic overlap has been observed with trisomy 3q [Falek et al., 1966; Wilson et al., 1978; Sciorra et al., 1979; Van Essen et al., 1991; Wilson et al., 1985; Holder et al., 1994] and a de novo balanced translocation t(3;17) [Ireland et al., 1991]. There are seven reports of autosomal dominant transmission of BDLS [Beck 1974; Kumar et al., 1985; Leavitt et al., 1985; Robinson et al., 1985; Reid et al., 1991; de Die-Smulders et al., 1992; Feingold and Lin, 1993] and in all cases, the phenotype is milder in expression than the phenotype associated with sporadic occurrence of this condition. Two instances of male-to-male transmission of BDLS have been reported [Halal and Silver, 1992; Chodirker and Chudley, 1994].

Our BDLS family differs in several important ways from those previously reported. The father, who has some signs of BDLS must be considered to be mildly affected, yet he has two severely affected children born of different mothers. These observations argue against the current thinking that autosomal dominant inheritance of BDLS is restricted to a milder expression of the phenotype. In that regard, our family represents the third reported case of male-to-male transmission but differs strikingly from the previous reports in that the male offspring in our case (patient A) was severely affected.

The cause of BDLS remains unknown. In our family a chromosomal abnormality is unlikely since all three affected members had a normal karyotype and the father and offspring present with radically different degrees of phenotypic expression. Autosomal recessive inheritance in our family is eliminated on the grounds that the offspring have different non-consanguineous and unrelated mothers. BDLS in our family is compatible with autosomal dominant inheritance. Expression of the milder phenotype in the father may result from mosaicism for the BDLS gene. Examples of mosaicism accounting for the recurrence of autosomal dominant disease is well documented in other conditions such as osteogenesis imperfecta [Cohn et al., 1990] and neurofibromatosis type 1 [Lazaro et al., 1994]. Paternal mosaicism could account for the inheritance of the more severe phenotype in the offspring since they would not have inherited the disease gene in mosaic form. Alternatively, the increased severity of BDLS in the second generation of our family calls to mind inheritance patterns found in anticipation syndromes such as Fragile X [Yu et al., 1991; Verkerk et al., 1991] and myotonic dystrophy [Harley et al., 1992; Brook et al., 1992] in which more severe manifestations are present in the offspring due to the expansion of unstable segments of repetitive DNA in successive generations.

Regardless of the underlying genetic mechanism, the findings in our family are important in that they argue against the views of familial BDLS 1) being exclusively maternally transmitted and 2) necessarily showing milder manifestations than are seen in sporadic cases.

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